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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/849,814

**Applicant(s)**

YOKOZEKI ET AL.

**Examiner**

Malgorzata A. Walicka

**Art Unit**

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,6,8,9,11 and 13-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6,8,9,11 and 13-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                                                        |                                                                                         |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

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The examiner acknowledges The Amendment and Request for Reconsideration filed June 8, 2006. Claim 4 has been previously cancelled; claims 2-3, 5, 7, 10 and 12, are cancelled by the current amendment. New claims 15-22 have been added. Claims 1, 6, 8-9, 11, 13 and 14 have been amended. Claims 1, 6, 8-9, 11, 13-22 are under examination.

### **DETAILED ACTION**

#### **1. Priority**

Acknowledgment is made of applicants' claim for priority based on application JP 2002-218958, filed 07/26/2002. Priority document has been filed, however, because the applicants have not provided translations it is uncertain whether the elected subject matter is disclosed. It is also unknown who is the author on the priority documents, and who is the assignee. Thus, the priority of the instant claims to JP 2002-218958, filed 07/26/2002, has not been granted.

#### **2. Objections**

Objections made in the Office action of Feb. 8, 2006 (previous action) to claim 11 and 13 for using the term "base sequence" to mean "nucleotide sequence" is withdrawn because the claims have been amended.

Objections to claims 6, 8, 11 and 13 made in the pervious action for designations of proteins by (C), (D), (G), (H), and DNA names (c), (b), (g) and (h) is withdrawn, because the claims have been amended.

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Objection to claim 2 made in the previous action is moot because the claim has been cancelled.

Claim 1 is objected to because in line 5 and in the last line it recites the term «enzyme-containing substrate » instead of « enzyme containing-substance » as in the fourth line of the claim.

In claim 8, please delete unnecessary «and» at the end of line 3.

### **3. Rejections**

#### **3.1. 35 USC, section 112, second paragraph**

Claims 6, 8, 11 and 13 were rejected in the previous action.

##### Rejection withdrawals

Claim 11 and 13 were rejected for lack of explicit listing the hybridization conditions. The rejection is now withdrawn because the claims have been amended.

Claims 6 and 8 were rejected for lack of definition of the term "inversion". This rejection is withdrawn because the term has been cancelled from the claims.

##### Rejection caused by amendment

Claim 1 and dependent claims 6, 8, 9, 11, 13-22 are rejected because it ends with the limitation "wherein said-enzyme containing substance comprises said enzyme" that is not a limitation because it is a tautology.

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Claims 6 and 8 and claims 15-16 and 17-18 are rejected as confusing in a redundant recitation of "having activity to use as substrates an amine component having two or more amino acid residues and a carboxy component, to form a peptide having one or more peptide bond than an amine component". The claims depend on claim 1 that already contains the recitation.

Claim 11 is lacking an antecedent for the recitation "said protein" in the second line, because the base claim 1 does not recite any protein. Depending claims 19 and 20 are included in the rejection.

### **3.2. 35 USC, section 112, first paragraph**

#### **3.2.1. Lack of written description**

Claim 1-3, 6, 8, 9, 11 and 13-14 were rejected in the previous action.

Rejection of claims 2 and 3 is moot because the claims have been cancelled.

#### Rejections withdrawn

Claims 1, 6, 8, 9, 11-14 were rejected in the previous action as directed to a genus of methods of producing peptides from any carboxy component or L-alanine ester and any amine component. This rejection is now withdrawn, because the claims have been amended.

Rejections maintained or caused by amendment

Claims 1, and claims 9 and 14 remain rejected as directed to a genus of methods using a genus of enzymes forming peptides comprising three or more amino acid residues. The genus is lacking sufficient written description of structure of the enzymes. The broadly claimed methods recite use of any peptide forming enzyme from any organism or man-made, whereas the disclosure provides only two species, i.e., the enzyme from *Sphingobacterium* identified by SEQ ID NO: 12 and SEQ ID NO: 6. Providing amino acid sequence set forth as SEQ ID NOs: 12 and 6 is not sufficient to identify the structure of the large genus of enzymes as a whole. One having skills in the art is not convinced that the Applicants were in possession of the claimed invention at the time the Application was filed.

In addition, claims 6 and 8 are rejected, because they are directed to a method of use of an enzyme which is an amino acid sequence having an amino acid sequence obtained from amino acid 21-619 or 1-619 of SEQ ID NO: 12 by substitution, deletion, insertion, and/or addition of one or a plurality of amino acids, and has the desired forming peptide activity.

The claims are directed to a large and variable genera of proteins the structure of which is not sufficiently disclosed in the specification and claims. The specification discloses only a single representatives for each of two claimed genera, which are polypeptides consisting of SEQ ID NO: 12 or amino acid 21-619 of SEQ ID NO: 12 (a mature form). Disclosing these two amino acid sequences is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within

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the claimed genera of polypeptides derived therefrom. No information, beyond the characterization of both genera functionally, i.e., as having peptide forming activity has been provided by Applicants. This limited characteristics does not indicate that Applicants had possession of the claimed genera of the modified polypeptides. The specification does not contain any disclosure of the structure of all variants, i.e., the polypeptide sequences derived from SEQ ID NO: 12, by substitution, deletion, insertion, and/or addition of one or a plurality of amino acids of SEQ ID No: 12 of its mature form. What is more important the disclosure fails to provide the relationship between function and structure of SEQ ID NO: 12. One skilled in the art realized that a change of even one amino acid residue the sequence can render the protein inactive or can change the type of enzymatic activity.

In summary, the predictability of the structure of the species of the claimed genera is not apparent and one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

#### Response to Applicants' arguments

In response to the rejection under 35 USC 112, for lack of written description and scope of enablement of the structure of the enzyme to be used in the claimed method, Applicants take position that the most important feature of the present invention is based on the finding that enzymatic reaction of the specific carboxy and amine component as defined in the present claim 1 enables significant production of tri-or longer peptide in the manner presented in formula on the top of page 10 REMARKS,

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page 9 second paragraph and page 10. Further Applicants admit that enzymatic methods of peptide production has been known in the art, however they require or costly raw materials or organic solvents, and has have low reaction yield, thus have not been appropriate for industrial use. Applicants go on arguing that the present invention is significantly more efficient and enables an industrial scale production of tripeptides with enzymatic reaction.

Applicants argument has bee fully considered but is found not persuasive for the following reasons:

- 1) Applicants do not address the reasons for rejection;
- 2) claim 1 is not directed to a method of production of tripeptides using formula A), wherein the method has high rection yield and threofore industrial application;
- 3) claim 1 is not directed to a method that does not require costly raw materials or organic solvents.

Without using a specific enzyme having identified structure, the broadly claimed method is not novel; see rejection under 35 USC 102, bellow.

### **3.2.2. Scope of enablement**

Rejection of claims 2-3 made in the previous Office Action is moot because the claims have been cancelled.

#### Rejection withdrawal

Claims 1-3, 6, 8, 9, 11-14 were rejected under this paragraph because

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although the specification is enabling for production of the peptides using L-alanine ester as the carboxy component and 24 compounds as amino components (Tables 17 and 18), the specification is not enabling for use of any amino component and any carboxy component. This rejection is now withdrawn, because the claims have been amended.

Rejections not withdrawn or caused by amendment

Claims 1 and dependent claims 9 and 14 were rejected in the previous action, because the specification, while being enabling for the method of using the enzyme of SEQ ID NO: 12 from the *Sphingobacterium*, does not reasonably provide enablement for using any enzyme having peptide forming ability. The reasons for the rejection are repeated bellow.

The nature and breath of the claimed invention encompasses a method of producing a peptide having three or more amino acid residues using an enzyme having peptide forming ability, wherein the enzyme is obtained from any natural or man-made sources. Although cloning DNA encoding enzymes, expressing them, testing the expressed proteins for the ability of peptide forming is well known in the art and the skills of artisans are highly developed, to make the invention as claimed, a skilled artisan is forced to experimentation which is not routine, absent teaching the structure of the enzyme to be used. Providing only one enzyme having the necessary activity, i.e., the enzyme identified by SEQ ID NO: 12, encoded by DNA of SEQ ID: 11, is not a sufficient instruction for obtaining any peptide forming enzyme, and leads to

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experimentation with a low probability of success. In result, without a further guidance on the part of Applicants with regards to the structure of the enzyme used in the claimed invention experimentation left to those having skills in the art is improperly extensive and undue.

Furthermore, claims 6 and 8 are rejected, because the specification, while being enabling for a method of use of an enzyme which is a protein set forth by SEQ ID NO: 12, or its mature form, does not reasonably provide enablement for a method of using an enzyme that is a modification of the SEQ ID NO: 12 or its mature form obtained by substitution, deletion, insertion and/or addition of one or a plurality of amino acids in amino acids. The reasons for rejection are repeated below.

The scope of the claims covers the use of any variant of the enzyme consisting of amino acid residues 21-619 of SEQ ID NO: 12 or any variant of SEQ ID NO: 12. Although techniques of modifications of amino acid sequences are well developed, and skills of artisans high, the lack of disclosure of function/structure of SEQ ID NO: 12 force one skilled in the art to experimentation which is not routine. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the protein variants have peptide forming ability. The provision of SEQ ID NO: 12 or amino acid residues 21-619 of SEQ ID NO: 12 fails to provide such guidance of polypeptides with major structural variations therefrom which remain encompassed within the scope of the rejected claims. Without a further guidance on the part of Applicants with regards to the

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structure of the variants of the enzyme to be used in the claimed method experimentation left to those skilled in the art has a low probability of success, thus it is improperly extensive and undue.

In addition, claims 11 and 13 and new claims 20 and 22 are rejected because the specification, while being enabling for a method of use of an enzyme encoded by the DNA molecule of SEQ ID NO: 11 encoding the enzyme of SEQ ID NO: 12, does not reasonably provide enablement for a DNA molecule that hybridizes under stringent conditions, which comprise hybridizing at 60 °C and 1 x SSC and 0.1% SDS, with a DNA molecule complementary to nucleotides 61-1917 or 121-1917 of SEQ ID NO: 11. The conditions described by Applicants as stringent are recognized by one having skills in the art of medium stringency. Such conditions select DNA molecules having 80%-90% identity to SEQ ID NO: 11, i.e., molecules with large modifications of structure. Accordingly, the invention as claimed requires from one having skills in the art an experimentation with a low probability of success, because it requires recruiting by hybridization an enormous number of DNA molecules, expressing them, testing their enzymatic activities and selecting those expressed proteins that retained the enzymatic activity. Without a further guidance, regarding the structural changes in SEQ ID NO: 11 that are neutral from the point of view of the function of the encoded polypeptide, the experimentation imposed on the skilled artisan is undue.

### **3.3. 35 USC 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless —(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Morihara et al. ( $\alpha$ -Chymotrypsin as the Catalyst of Peptide Synthesis, Biochem. J. 163, 531-542, 1977, enclosed in IDS).

The claims are directed to an enzymatic method of producing a peptide having three or more amino acid residues wherein the enzyme is any enzyme having a peptide forming activity, or enzymes obtained from amino acid sequence of SEQ ID NO:12 or its mature form ( amino acids 21-619 by plurality of substitutions, deletions, insertions or additions, wherein the enzyme uses:

a) as the carboxy component for synthesis

1) amino acid ester or

2) amino acid amide;

b) as an amine component

1) unprotected peptide of two or more amino acids

2) C-protected peptide having two or more amino acids

3) a peptide having two or more amino acids

4) a peptide having two or more amino acids and a C-terminal amine in place of an amino acid.

Morihara et al. disclose production of tripeptide AC-Phe-Gly-Ala by an enzyme alpha chymotrypsin from Ac-Ph-OEt (carboxy component, amino acid ester) and Gly-Ala (amino component, unprotected peptide having two amino acid residues); see Table 4, second row. Chymotrypsin is an enzyme having a peptide forming activity and its sequence may be obtained from amino acid sequence of SEQ ID NO:12 or its mature form (amino acids 21-619) by plurality of substitutions, deletions, insertions or additions. The invention taught by Morihara et al. is that of claims 1, 6 and 8 of the instant application.

#### 4. Conclusion

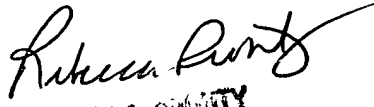
All claims are rejected.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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